The Pending Claims

Claims 1-14, 17-28, 40-47 and 50-53 are currently pending. Claims 1-14 are directed to the universal bystander cell line, whereas claims 17-21 are directed to the composition comprising the universal bystander cell line and a cancer antigen, claims 22-28 are directed to the method of making the universal bystander cell line, claims 40-47 are directed to the method of stimulating an immune response, and claims 50-53 are directed to the improved method of cancer immunotherapy.

The Office Action

The Office has rejected all of the pending claims under 35 U.S.C. § 112, first paragraph, for alleged lack of description and alleged lack of enablement. Reconsideration is hereby requested.

Discussion of Rejections under Section 112, first paragraph

The Office has rejected all of the pending claims for alleged lack of description. This rejection is traversed for the reasons set forth below.

According to the Office, the specification lacks description of cells and cell lines that (i) naturally lack MHC-I and MHC-II antigens, (ii) are characterized by the absence of B-lymphocyte markers of immunoglobulin and an Epstein-Barr viral genome and associated nuclear antigen, and (iii) are derived from a blast crisis of chronic myeloid leukemia. Yet, the K562 cell line has all of these characteristics. Furthermore, Applicants have taught that ANY human cell line that naturally lacks MHC-I and MHC-II antigens and can be modified to express at least 500 ng GM-CSF/10^6 cells/24 hours in accordance with the teachings of the specification can be used (see, also, the specification at, for example, pg. 6, line 28, through pg. 7, line 3). Whether or not a given human cell line naturally lacks MHC-I and MHC-II antigens is readily ascertainable -- either the human cell line expresses MHC-I and/or MHC-II or it does not. Numerous examples of such cell lines were known in the art prior to the February 2, 1998, the date to which the instant application claims priority. See, e.g., SK-MEL-33 (Wang et al., J. Clin. Invest. 91: 684-692 (1993)), and other melanoma (Ferrone et al., Immunol. Today 16 (10): 487-494 (1995); Kageshita et al., Cancer Res. 53 (14): 3349-3354 (1993); and Wang et al., Tissue Antigens 47 (5): 382-390 (1996); abstracts attached) and cervical cancer cell lines. It is well-established that Applicants need not describe that which is known in the art.

The Office also contends that the specification lacks description as to what is the improvement with respect to the claimed method of cancer immunotherapy. Applicants disagree. The improvement is the administration of the present inventive irradiated composition comprising the universal bystander cell line and an antigen of the cancer to be treated as recited in claims 50-53 and as supported by the instant specification in its entirety.

Further contended by the Office is that the specification does not indicate as to which specific cancer therapy the instant invention can be applied. Yet, the Office admits otherwise on page 6 of the Office Action. The specification at, for example, paragraph [0051] teaches that any type of cancer can be treated in accordance with the present invention. The specification further teaches that the present inventive method has applicability as a local adjuvant therapy for resected cancers as well as a local control of tumor growth, such as carcinomas of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, rectum and stomach, and as a treatment of a sarcoma, e.g., fibrosarcoma or rhabdosarcoma, a hematopoietic tumor of lymphoid or myeloid lineage, or another tumor, such as melanoma, teratocarcinoma, neuroblastoma or glioma. The very nature of the present invention is that it is universally applicable to the treatment of all cancers. The administration of the universal bystander cell line to a human patient having cancer results in the production of GM-CSF, which stimulates an immune response against the cancer (see, e.g., paragraph [0019]). The administration of the antigen of the cancer to be treated is what renders the treatment specific to a given cancer. It is the combined administration of the universal bystander cell line and the antigen of the cancer to be treated that results in the adequate recruitment of APCs and the successful priming of the immune system against the cancer to be treated. The advantage of such a method is that it obviates the need to culture and transduce autologous tumor cells for each and every patient (as explained, for example, in paragraph [0019] of the instant specification).

For the above reasons, Applicants submit that the claims do not lack description. Accordingly, Applicants request the withdrawal of this rejection.

The Office has rejected all of the pending claims for alleged lack of enablement. This rejection is traversed for the reasons set forth below.

According to the Office, the specification does not teach which cell or cell line naturally lacks MHC-I and MHC-II nor the source of obtaining the cell line. As indicated above, whether or not a given human cell line naturally lacks MHC-I and MHC-II antigens is readily ascertainable -- either the human cell line expresses MHC-I and/or MHC-II or it does not. Numerous examples of such cell lines were known in the art prior to the February 2, 1998, the date to which the instant application claims priority. See, e.g., SK-MEL-33 (Wang et al., J. Clin. Invest. 91: 684-692 (1993)), and other melanoma (Ferrone et al., Immunol. Today 16 (10): 487-494 (1995); Kageshita et al., Cancer Res. 53 (14): 3349-3354 (1993); and Wang et al., Tissue Antigens 47 (5): 382-390 (1996); abstracts attached) and cervical cancer cell lines. It is well-established that Applicants need not teach that which is known in the art.

The Office also contends that it is unclear if the K562 cell line expresses MHC-I and/or MHC-II. Applicants disagree. The fact that K562 naturally lacks MHC-I and MHC-II is clear from Example 1 and from the references cited in paragraph [0020].

Further contended by the Office is that the specification fails to teach how to target different cancers. Yet, contrary to what is assumed by the Office, targeting is not required by the present invention. As explained above, the administration of the universal bystander cell line to a human patient having cancer results in the production of GM-CSF, which stimulates an immune response against the cancer (see, e.g., paragraph [0019]). It is the ensuing immune response generated by the vaccine that targets the tumor. The administration of the antigen of the cancer to be treated is what renders the treatment specific to a given cancer. It is the combined administration of the universal bystander cell line and the antigen of the cancer to be treated that results in the adequate recruitment of APCs and the successful priming against the cancer antigen.

Still further contended by the Office is that the specification fails to teach how to escape the immune response of the patient so that the introduced bystander cell line can continuously produce GM-CSF. Here, again, the Office assumes that continuous expression of GM-CSF is necessary for the present invention to be effective. Such is not the case. Only initial GM-CSF expression is necessary to stimulate an immune response against the cancer. In fact, short-term gene expression is actually desirable in the context of cancer immunotherapy. The effectiveness of the present invention is evidenced by the data set forth in Figure 4. While the Office cites Verma et al. in support of its position, Applicants point out that Verma et al. is directed to gene therapy, specifically stable gene replacement therapy, whereas the present invention is not. The present invention actually avoids the problems of gene therapy by providing for uniformly high expression of GM-CSF through the use of a universal bystander cell line, thereby avoiding the issues of gene transfer and expression of functional protein presented by gene therapy. In this regard, Applicants point to Hwang et al., Seminars in Oncology 26(2): 192-201 (April 1999), reference AT in IDS, which also evidences the advanced state of the art of cancer immunotherapy (see, e.g., page 196, right column, through page 197, left column).

The Office states that the claims read on xenograft transplantation and then goes on to cite Parker et al. in supports of its position of lack of enablement with respect to same. Yet, Applicants note that the method claims are directed to cancer -- not xenograft transplantation.

Applicants assert that Example 2 exemplifies the use of a universal bystander cell line *in vivo* in accordance with the present invention (see page 20, lines 12-13). The universal bystander cell line used in Example 2 of the instant specification is K562, which is derived from a lymphoblast crisis of chronic myeloid leukemia (see ATCC CCL-243). As disclosed in the instant specification at page 7, lines 4-9, the universal bystander lacks MHC antigens. Example 2 directly compares the efficacy of the universal bystander cell line lacking MHC antigen expression, i.e., the K562 cell line, with the efficacy of irradiated GM-CSF-expressing tumor cells in Figure 4 of the specification, for example.

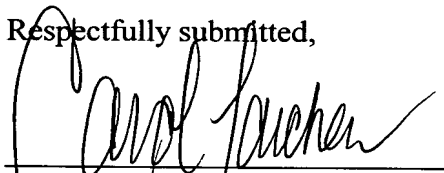
Accordingly, Applicants take exception to the Office's characterization of the specification as teaching only "what is intended to be done" but not actually teaching "how to do that which is intended" (Office Action, paragraph bridging pp. 7-8). The specification is replete with teachings as to how to make and use the universal bystander cell line and a composition comprising the same and an antigen of a cancer to be treated (see, e.g., paragraph [0020] through paragraph [0053] and the examples). Consequently, it cannot be said that the ordinarily skilled artisan would have to engage in an undue amount of experimentation without a reasonable expectation of success in order to practice the claimed invention.

In view of the foregoing, Applicants submit that the claims are enabled. Therefore, Applicants request the withdrawal of this rejection.

Conclusion

In view of the above, the application is considered to be in good and proper form for allowance, and the Office is respectfully requested to pass this application to issuance. If, in the opinion of the Office, a telephone conference would expedite prosecution, the Office is encouraged to contact the undersigned attorney.

Respectfully submitted,



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